Claims 1-15, 18-44, 47-72, 75-92, 95-102, 104-112, 115-122, 124-132, and 135-163 are pending.

Claims 16-17. 45-46, 73-74, 93-94, 103, 113-114, 123, and 133-134 were previously canceled.

Claims 3-11, 19-24, 32-40, 48-53, 60-68, 76-81, 88-91, 96-101, 108-111, 116-121, 128-131, 136-141 and 148-150 have been withdrawn from consideration due to the election-of-species requirement set forth in the Office Action mailed on April 11, 2003.

Claims 1-2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, 142-147, and 151-163 are currently under examination.

Independent claims 1, 30, 58, 86, 106, and 126 have each been currently amended to state that when the low solubility drug is basic, the solubility improved form of the drug has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form. Support is in the specification at page 10, lines 11-15.

The Invention

The invention relates to compositions that increase the concentration of low solubility drugs, i.e., those having an aqueous solubility less than about 1 mg/mL. The solubility-improved form of the drug when dissolved in the use environment provides an initial concentration of drug that exceeds the equilibrium concentration of drug, while the concentration-enhancing polymer retards the rate at which the initially enhanced drug concentration falls to the equilibrium concentration. See page 12, lines 22-28 of the specification.

The §112 Rejection

Withdrawal of the rejection under 35 USC §112 is acknowledged with gratitude.

The §102 Rejection Over Miyajima

Claims 1-2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, and 142-145 were rejected over Miyajima, US 4,983,593. Miyajima discloses a pharmaceutical composition comprising NZ-105 and HPMCAS, NZ-105 itself being in the form of a hydrochloride. The rejection is traversed, particularly considering the claims as they have been currently amended. The claims require that when the low solubility

drug is basic, the solubility improved form of the drug has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form. By this language, the claims thus exclude the hydrochloride as a solubility improved form. Even assuming that the hydrochloride disclosed in Miyajima is more soluble than the NZ-105 free base, Applicants' claims require a solubility-improved form that is more soluble than the chloride as well. Thus Miyajima, disclosing as it does only the hydrochloride salt form, is outside the scope of Applicants' claims and cannot be anticipatory. Withdrawal of the rejection is accordingly respectfully requested.

The §102 Rejection Over Dunn

Claims 1-2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75, 82-85 were rejected under 35 USC 102(b) as being anticipated by Dunn, US 4,461,759. The rejection is traversed based on the fact that verapamil hydrochloride, the form of verapamil disclosed in Dunn, is a highly soluble drug, in contrast to the Examiner's statement that verapamil is a low solubility drug. Dunn himself, in addition to stating that verapamil has a solubuility of 100 g/mL (column 2, bottom three lines) alludes at column 1, lines 15-19 to the problem of high solubility when he states

> For such products, controlling their rate of salvation after ingestion also influences their rate of absorption, and drugs which are highly or moderately water-soluble present special formulation problems.

See also The Merck Index, 13th edition, pages 1771-1772, copy included herewith. The Merck index cites verapamil hydrochloride as having a solubility in water of 83 mg/mL. That is a very high solubility, well beyond the upper limits of aqueous solubility imposed by Applicants in their claims. From the context of Dunn, his invention concerns making a controlled release dosage form of verapamil hydrochloride that meters out verapamil at a constant rate because verapamil hydrochloride has such a high aqueous solubility. Thus Dunn would not suggest a physical mixture of a low solubility drug and a concentration enhancing polymer. Rather it would suggest a dosage form that is meant to dampen the high aqueous solubility of verapamil.

The §102 rejection over Okada

Per paragraphs 4 and 5 of the Office Action, claims 1-2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135 and 142-145 continue to be rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al. (US 5,496,561).

In particular, the Examiner commented as follows

> Although Okada does not disclose examples of composition that contains CAP, it is respectfully noted that, a prior art does not have to exemplify all the different embodiments. There is however a disclosure of CAP with a drug. Specifically, page 10, line 23 to page 11, line 12 of the instant specification and paragraph [0029] of the published application states that combination "as used herein means that the solubility-improved form and concentration-enhancing polymer may be in physical contact with each other or in close proximity but without the necessity of being physically mixed. For example, the solid composition may be in the form of a multi-layer tablet, as known in the art, wherein one or more layers comprises the solubility-improved form and one or more different layers comprises the concentration-enhancing polymer. Yet another example may constitute a coated tablet wherein either the solubility-improved form of the drug or the concentration-enhancing polymer or both may be present in the tablet core and the coating may comprise the solubility-improved form or the concentration-enhancing polymer or both. Alternatively, the combination can be in the form of a simple dry physical mixture wherein both the solubility-improved form and concentration-enhancing polymer are mixed in particulate form and wherein the particles of each, regardless of size, retain the same individual physical properties that they exhibit in bulk. Any conventional method used to mix the polymer and drug together such as physical mixing and dry or wet granulation, which does not substantially convert the drug and polymer to a molecular dispersion, maybe used." Thus, contrary applicants' assertion, coatings are not excluded by the combination or the physical mixing does not exclude coating. Maximum drug concentration (claim 1), which is the area under the curve (claim 30) is a property of the composition and in this case the composition is generic to a combination of drug and polymer (concentration-enhancing polymer). Examiner has not juxtaposed Okada on applicants' specification. Rather, the claims are directed to broad subject matter of drug combined with any of the polymers recited. [Pages 6-7 of the Office Action].

The Examiner appeared to be arguing that Okada's disclosure of CAP being used in a membrane surrounding a core containing his drug constitutes a "physical mixture" within the scope of Applicants' claims. Applicants disagree with that interpretation. How or why the Examiner equated a physical mixture (in which a concentration enhancing polymer and low solubility drug are mixed) with Okada's membrane-coated device (in which the drug is in a core surrounded by, but not physically mixed with, a membrane containing the polymer) is not understood. That interpretation goes against what one skilled in the art understands a physical mixture to be, and is in no way supported by the portion of Applicants' specification that was quoted by the Examiner. That quotation is directed to explaining the meaning of the term "combination", and disclosed, *inter alia*, that a physical mixture is one form of a "combination". But, there is no basis in that quotation for concluding that "physical mixture" includes any embodiment in which, like Okada, a drug contained in a core is surrounded by a membrane containing a polymer.

The very language cited by the Examiner from Applicants' specification in fact supports that Okada disclosed no embodiment that is a physical mixture of a low solubility drug and one of Applicants' required concentration-enhancing polymers. The full quotation (page 10, line 23 to page 11, line 12) defines what is meant by the broad term "combination". It explains that a physical mixture is an embodiment within the scope of "combination". The first clause quoted by the Examiner, namely

> [combination] "as used herein means that the solubility improved form and concentration-enhancing polymer may be in physical contact with each other or in close proximity **but without the necessity of being physically mixed**." [Emphasis supplied]

indicates that some embodiments of a "combination" are not physically mixed (hence they cannot be not physical mixtures).

The second and third sentences of the quotation describe examples of "combinations":

> For example, the solid composition may be in the form of a multi-layer tablet, as known in the art, wherein one or more layers comprises the solubility-improved form and one or more different layers comprises the concentration-enhancing polymer. Yet another example may constitute a coated tablet wherein either the solubility-improved form of the drug or the concentration-enhancing polymer or both may be present in the tablet core and the coating may comprise the solubility-improved form or the concentration-enhancing polymer or both.

The fourth sentence of the quotation, by its use of the transition "Alternatively", signals that something different (i.e., a physical mixture) is about to be disclosed. The text then goes on to describe physical mixtures and how physical mixing can be achieved:

> Alternatively, the combination can be in the form of a simple dry physical mixture wherein both the solubility-improved form and concentration-enhancing polymer are mixed in particulate form and wherein the particles of each, regardless of size, retain the same individual physical properties that they exhibit in bulk. Any conventional method used to mix the polymer and drug together such as physical mixing and dry or wet granulation, which does not substantially convert the drug and polymer to a molecular dispersion, may be used.

There is nothing in the any of the above passages indicating that a drug in a core surrounded by a membrane constitutes a physical mixture. The full text of the quotation simply reviews different forms of a "combination". The Examiner is accordingly urged to reconsider her interpretation and to withdraw the rejection over Okada.

Applicants otherwise continue to traverse the rejection on the basis presented in their previous response (responding to the Office Action mailed on February 8, 2005), the arguments against the rejection over Okada being incorporated herein by reference.

The §102 and §103 Rejections Over Bymaster

Claims 1, 30, 58, 86, 126, and 156-161 were rejected under §102(e) as anticipated by Bymaster, US 6,147,072. Claims 146, 147, 151-155, 162, and 163 were rejected under §103(a) as obvious over Bymaster. Bymaster is insufficient to support either rejection, for the reasons that follow.

It is believed that the rejection is based at least in part on the contention that "physical mixing of polymers (some of which are enteric) does not exclude enteric–coated dosage form", as stated by the Examiner in Paragraph 7 of the Office Action. For all of the reasons discussed above in traversing the rejection over Okada, Applicants respectfully submit that the term "physical mixture" does indeed exclude an embodiment wherein the polymer is in a coating and the drug is incorporated into a core, the arguments being incorporated by reference .

Bymaster otherwise discloses that some of the polymeric components useful in Applicants' invention are known. But, for the reasons discussed above in traversing the rejection over Okada, Applicants traverse the rejection over Bymaster. Bymaster never discloses, describes or suggests a composition in which one of the specific polymers in Applicants' claims is physically mixed with a solubility-improved drug. Bymaster simply discloses certain polymers for use in making an enteric dosage form, i.e., one coated with an enteric polymer that will allow it to pass through the (acid) upper GI tract. But, enterically coated dosage forms are not physical mixtures. Because Bymaster never discloses a composition within the scope of Applicants' claims, Bymaster cannot anticipate.

Bymaster never otherwise discloses anything relating to any composition that is a physical mixture of one of Applicants' polymers and a solubility-improved drug. There is not even a bare suggestion to make, or any motivation for making, such a physical mixture. It is well accepted that in order for an obviousness rejection to lie, the prior art must in some way supply a suggestion to do that which Applicant has invented, and must also provide a reasonable expectation of success. . American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the

'prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Bymaster suggests neither the composition, any reason for making one, or any expectation of success. Thus Bymaster is insufficient, in fact and in law, to support an obviousness rejection.

It is accordingly respectfully requested that the rejections over Bymaster be withdrawn.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

Date: December 5, 2005

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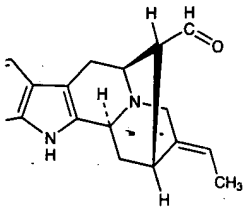
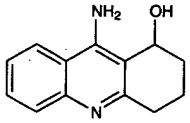
aine. [6874-98-2] Sarpagan-17-ol, mol wt 292.37. C 78.05%, H 6.[illegible] from bark of *Geissosperum vellosii* oport *et al.*, *J. Am. Chem. Soc.* [illegible] Rapoport, Moore, *J. Org. Chem.* [illegible] *l., Tetrahedron* **19,** 2241 (1963).



thanol, mp 305-306°. Can be [illegible]. $[\alpha]_D^{26}$ +48°. uv max (ethanol): [illegible]

ine. [104675-29-8] 9-Amino-1,2,3,4-[illegible] $C_{13}H_{14}N_2O$; mol wt 214.26. C 72.[illegible] O 7.47%. Cognition enhancing [illegible]; major metabolite of tacrine. [illegible] . Pierrat, **EP 179383**; *eidem*, **US** [illegible] ast-Roussel); G. M. Shutske *et al.*, [illegible] 38); *eidem, ibid.* **32,** 1805 (1989); [illegible] . K. Puri *et al., J. Clin. Pharmacol.* [illegible] gy: M. F. M. Braga *et al., Brit. J.* [illegible] 991). Structure-activity study: D. A. [illegible] ari, *Biochem. Biophys. Res. Commun.* [illegible] determn in biological fluids: R. S. [illegible] 94, 347 (1989). Clinical evaluation [illegible] . F. Murphy *et al., Ann. N.Y. Acad. Sci.* [illegible]



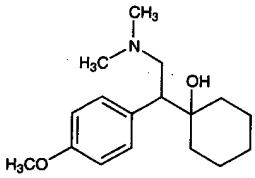
9-22-1] HP-029; Mentane. [illegible] 330.33. Crystals from methanol [illegible] °. LD_{50} in mice (mg/kg): 136 [illegible] 989).
otropic.

Turpentine. Larch turpentine, [illegible] Mill. (*L. europaea* Lam. & DC.), [illegible] Southern Europe. *Constit.* [illegible] nicroscopy: D. A. Johansen, *Plant* [illegible] Hill, New York, 1940) pp 115-116. s greenish, limpid, tenacious, [illegible] dor; hot, pungent, somewhat [illegible] rittle on prolonged exposure to [illegible] l acetic acid, amyl alcohol, acetone, [illegible] reely sol in alc.
agent and mounting medium for [illegible]

ine. [93413-69-5] 1-[2-(Dimethyl[illegible] ethyl]cyclohexanol; (±)-1-[α-[illegible] thoxybenzyl]cyclohexanol; *N,N*-[illegible] lexyl)-2-(4-methoxyphenyl)ethyl[illegible] NO_2; mol wt 277.40. C 73.61%, [illegible] Serotonin noradrenaline reuptake [illegible] E. M. Husbands *et al.*, **EP** [illegible] both to Am. Home Prods.); and [illegible] dley *et al., J. Med. Chem.* **33,** 2[illegible] idies: E. A. Muth *et al., Biochem.* [illegible] 86). HPLC determn in biological [illegible]

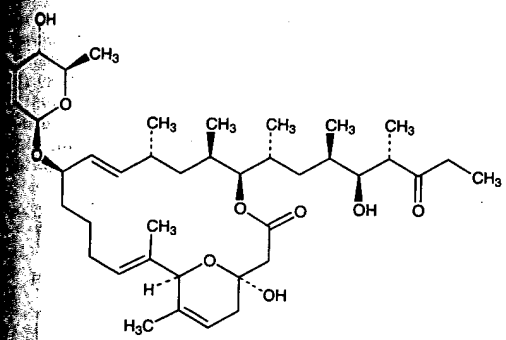
on.

Hicks *et al., Ther. Drug. Monitor.* **16,** 100 (1994). Clinical cokinetics: K. J. Klamerus *et al., J. Clin. Pharmacol.* (1992). Clinical trial in major depression: E. Schweizer *J. Clin. Psychopharmacol.* **11,** 233 (1991). Review of cology and clinical efficacy in depression: S. A. Mont- *J. Clin. Psychiatry* **54,** 119-126 (1993). Clinical trial ralized anxiety disorder: A. J. Gelenberg *et al., J. Am. Assoc.* **283,** 3082 (2000).



rochloride. [99300-78-4] Wy-45030; Effexor. C_{17}-O)$_n$HCl; mol wt 313.87. White to off-white crystalline om methanol/ethyl acetate, mp 215-217°. Soly (mg/ml): ter. Partition coefficient (octanol/water): 0.43.
Form. Crystals from ethyl acetate, mp 102-104°. 27.6° (c = 1.07 in 95% ethanol).
Form hydrochloride. Wy-45655. Crystals from meth- her, mp 240-240.5°. $[\alpha]_D^{25}$ −4.7° (c = 0.945 in ethanol).
Form. Crystals from ethyl acetate, mp 102-104°. 27.1° (c = 1.04 in 95% ethanol).
Form hydrochloride. Wy-45651. Crystals from meth- her, mp 240-240.5°. $[\alpha]_D^{25}$ +4.6° (c = 1.0 in ethanol).
AP CAT: Antidepressant.

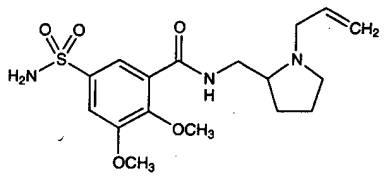
Venturicidins. Antifungal antibiotics isolated from myces *aureofaciens* strains. Preliminary isolation work: *et al., Nature* **192,** 952 (1962). Isoln of venturicidins A and activity studies: Brufani *et al., Helv. Chim. Acta* **51,** (1968); *see also* Langcake *et al., Biochem. Soc. Trans.* **2,** 974). Final structures: Brufani *et al., Experientia* **27,** 604 *eldem, Helv. Chim. Acta* **55,** 2329 (1972).



Venturicidin A R = NH_2CO
Venturicidin B R = H

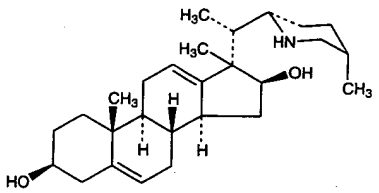
uricidin A. [33538-71-5] Venturicidin B 3′-carba- $C_{41}H_{67}NO_{11}$; mol wt 749.97. Needles from chloroform- her, mp 145-147°. Also reported as mp 140-142°. $[\alpha]_D$ (c = 0.5 in chloroform). uv max (alcohol): 206, 247 ker), ~300 nm (shoulder) (log ε 3.80, 2.23, 2.08).
uricidin B. [33538-72-6] (3-Decarbamoyloxy)-3-hy- enturicidin A. $C_{40}H_{66}O_{10}$; mol wt 706.94. Amorphous powder from chloroform-ether, mp 168-170°. Also re- as mp 145-149° (ethyl acetate-petr ether). $[\alpha]_D$ +100° 0.847 in chloroform).

10. Veralipride. [66644-81-3] 5-(Aminosulfonyl)-2,3- hoxy-*N*-[[1-(2-propenyl)-2-pyrrolidinyl]methyl]benzamide; *N*-[(1-allyl-2-pyrrolidinyl)methyl]-5-sulfamoyl-*o*-veratramide; LIR-1660; Agréal; Agradil; Veralipril. $C_{17}H_{25}N_3O_5S$; mol wt 383.47. C 53.25%, H 6.57%, N 10.96%, O 20.86%, S 8.36%. Prepn: **NL 7707982** (1978 to Soc. d'Etudes Sci. Ind. de l'Ile-de-France), *C.A.* **89,** 30768 (1978). Pharmacological studies: P. Bouyard *et al., Sem. Hop.* **56,** 1475 (1980); J. C. Czyba, *ibid.* 1483. Clinical studies: R. Renaud, J. Macler, *ibid.* **57,** 353 (1981); S. Angeli, P. Fougère, *ibid.* **58,** 111 (1982).



THERAP CAT: Treatment of menopausal disorders.

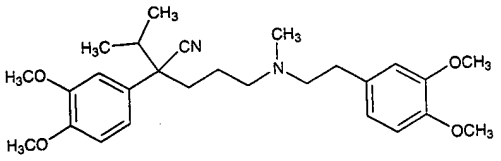
10011. Veralkamine. [17155-31-6] (3β,16β,17α,22α)-17-Methyl-18-nor-16,28-secosolanida-5,12-diene-3,16-diol; 17-methyl-20α-((2*S*,5*S*)-5-methyl-2-piperidyl)-18-nor-17α-pregna-5,12-diene-3β,16β-diol; (22*S*:25*S*)-12,26-epimino-17β-methyl-18-norcholesta-5,12-diene-3β,16β-diol; (17*S*:12*S*:25*S*)-22,26-epimino-18(13 → 17)-*abeo*-cholesta-5,12-diene-3β,16β-diol; veralcamine. $C_{27}H_{43}NO_2$; mol wt 413.63. C 78.40%, H 10.48%, N 3.39%, O 7.74%. Steroidal alkaloid isolated from *Veratrum album* sp. *lobelianium* (Bernh.) Suessenguth, *Liliaceae:* Tomko *et al., Pharm. Zentralhalle* **99,** 373 (1960), *C.A.* **55,** 2013e. Structure studies: Tomko *et al., Coll. Czech. Chem. Commun.* **27,** 1404 (1962). Complete structure: Tomko *et al., Tetrahedron Letters* **1967,** 3907; *eidem, Tetrahedron* **24,** 4865 (1968); Hoehne *et al., ibid.* 4875.



Crystals from ethanol, mp 119-123° and 165-169°; $[\alpha]_D^{24}$ −84.1 ±3° (c = 0.533 in $CHCl_3$).
***N,O,O*-Triacetate.** mp 152-154°. $[\alpha]_D^{27}$ −8.0° ($CHCl_3$).
***N*-Monoacetate.** mp 191-193°. $[\alpha]_D^{23}$ −79.1° ($CHCl_3$).

10012. Verapamil. [52-53-9] α-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)benzeneacetonitrile; 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile; α-isopropyl-α-[(*N*-methyl-*N*-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitrile; iproveratril; D-365. $C_{27}H_{38}N_2O_4$; mol wt 454.60. C 71.33%, H 8.43%, N 6.16%, O 14.08%. Prototype calcium antagonist; vasodilating activity resides primarily in the (*S*)-isomer. Both isomers inhibit the p-glycoprotein efflux pump in multidrug resistant tumor cells. Prepn: **BE 615861**; Dengel, **US 3261859** (1962, 1966 both to Knoll). Pharmacology: H. Haas, G. Härtfelder, *Arzneimittel-Forsch.* **12,** 549 (1962). Physical and chemical data: W. Appel, *ibid.* 562. Synthesis and absolute configuration of enantiomers: H. Ramuz, *Helv. Chim. Acta* **58,** 2050 (1975). Stereospecific synthesis: L. J. Theodore, W. L. Nelson, *J. Org. Chem.* **52,** 1309 (1987). HPLC determn of enantiomers and metabolites in plasma: G. Stagni, W. R. Gillespie, *J. Chromatog. B* **667,** 349 (1995). Comprehensive description: Z. L. Chang, *Anal. Profiles Drug Subs.* **17,** 643-674 (1988). Review of pharmacology and therapeutic use in arrhythmias: B. N. Singh *et al., Drugs* **25,** 125-153 (1983); in hypertension: D. McTavish, E. M. Sorkin, *ibid.* **38,**

19-76 (1989). Clinical trial of dexverapamil as adjunct to cancer chemotherapy: G. Kornek *et al.*, *Cancer* **76,** 1356 (1995); R. J. Motzer *et al.*, *J. Clin. Oncol.* **13,** 1958 (1995).



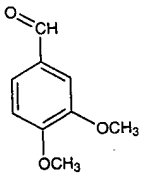
Viscous, pale yellow oil. $bp_{0.01}$ 243-246°. n_D^{25} 1.5448. Practically insol in water. Sparingly sol in hexane; sol in benzene, ether. Freely sol in the lower alcohols, acetone, ethyl acetate, chloroform.

Hydrochloride. [152-11-4] Arpamyl; Berkatens; Calan; Cardiagutt; Cardibeltin; Cordilox; Covera-HS; Dignover; Drosteakard; Geangin; Isoptin; Quasar; Securon; Univer; Vasolan; Veracim; Veramex; Veraptin; Verelan; Verexamil. $C_{27}H_{38}N_2O_4$.HCl; mol wt 491.07. Crystals, dec 138.5-140.5° (corr). pH of 0.1% aq soln: 5.25. uv max: 232, 278 nm. Soly (mg/ml): water 83, ethanol (200 proof) 26, propylene glycol 93, ethanol (190 proof) >100, methanol >100, 2-propanol 4.6, ethyl acetate 1.0, DMF >100, methylene chloride >100, hexane 0.001. pKa 8.6. LD_{50} in mice, rats (mg/kg): 7.6, 16 i.v.; 68, 107 s.c.; 68, 67 i.p.; 163, 114 orally (Haas, Härtfelder).

(*R*)-Form hydrochloride. [38176-02-2]; [38321-02-7]. Dexverapamil hydrochloride. Crystals, mp 131-133°. $[\alpha]_D^{25}$ +8.9° (c = 5.01 in ethanol).

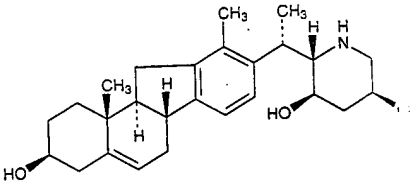
THERAP CAT: Antihypertensive; antianginal; antiarrhythmic (class IV).

10013. Veratraldehyde. [120-14-9] 3,4-Dimethoxybenzaldehyde; 3,4-dimethoxybenzenecarbonal; veratric aldehyde; protocatechualdehyde dimethyl ether. $C_9H_{10}O_3$; mol wt 166.17. C 65.05%, H 6.07%, O 28.88%. Prepd by methylation of vanillin: Kostanecki, Tambor, *Ber.* **39,** 4022 (1906); Buck, *Org. Syn.* **13,** 102 (1933); Alt, US **3007968** (1957 to Monsanto); by oxidation of veratryl alcohol with chromium(VI) oxide-pyridine complex: Holum, *J. Org. Chem.* **26,** 4814 (1961).



Needles from ether, petr ether, toluene, or carbon tetrachloride. Odor of vanilla beans; mp 42-43°; bp_{760} 281°; bp_{53} 201°; bp_{10} 155°. Slightly sol in hot water; freely sol in alcohol and ether. Solns are oxidized to veratric acid under the influence of light.

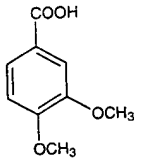
10014. Veratramine. [60-70-8] (3β,23β)-14,15,16,17-Tetradehydroveratraman-3,23-diol. $C_{27}H_{39}NO_2$; mol wt 409.60. C 79.17%, H 9.60%, N 3.42%, O 7.81%. Secondary base from *Veratrum grandiflorum* (Maxim.) Loes. f., and from *V. viride* Ait., *Liliaceae*. Isoln and structure: Saito, *Bull. Chem. Soc. Japan* **15,** 22 (1940); Jacobs, Craig, *J. Biol. Chem.* **160,** 555 (1945); Jacobs, Sato, *ibid.* **181,** 55 (1949); **191,** 71 (1951); Tamm, Wintersteiner, *J. Am. Chem. Soc.* **74,** 3842 (1952); Wintersteiner, *Festschrift Arthur Stoll* (Birkhäuser-Verlag, Basel) pp 166-176. Total synthesis: Masamune *et al.*, *J. Am. Chem. Soc.* **89,** 4521 (1967); Johnson *et al.*, *ibid.* 4523; Masamune *et al.*, *Tetrahedron* **27,** 3369 (1971); Kutney *et al.*, *Can. J. Chem.* **53,** 1796 (1975). Stereochemistry: Sicher, Tichy, *Tetrahedron Letters* **1959**(12), 6 (1959); Kataoka, *Chem. & Ind. (London)* **1961,** 512; Bailey *et al.*, *Tetrahedron Letters* **1963,** 555. Revised stereochemistry: Scott *et al.*, *ibid.* **1967,** 2381; Kupchan, Suffness, *J. Am. Chem. Soc.* **90,** 2730 (1968); Sprague *et al.*, *Tetrahedron* **27,** 4857 (1971). *See also:* Veratrum Viride.



Crystals, mp 206-207°. Slightly sol in water. Sol in alcohol. Precipitated by digitonin. $[\alpha]_D^{25}$ −71.8° to $[\alpha]_D^{25}$ −70° (c = 1.56 in methanol). uv max: 268 nm.

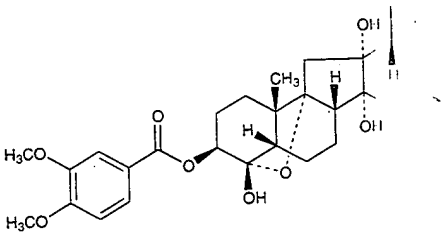
Dihydroveratramine. Crystals, mp 192.5-194° (c = 1.26 in acetic acid).

10015. Veratric Acid. [93-07-2] 3,4-Dimethoxybenzoic acid; dimethylprotocatechuic acid. $C_9H_{10}O_4$; mol wt 182.17. C 59.34%, H 5.53%, O 35.13%. Isolated from seed of *Sabadilla caulon officinale* (Schlecht. & Cham.) A. Gray (*Sabadilla officinarum* Brandt). Prepn: Arthur, Ng, *J. Chem. Soc.* [illegible]



Monohydrate. Odorless crystals. At 100° becomes anhydr, mp 180-181° when anhydr. Sublimes in rhombic crystals. Sol in 2150 parts cold, 165 parts boiling water; very sol in alcohol or ether. Its barium salt is but slightly sol in water.

10016. Veratridine. [71-62-5] (3β,4α,16β)-cevane-3,4,12,14,16,17,20-heptol 3-(3,4-dimethoxybenzoate) 3-veratroylveracevine. $C_{36}H_{51}NO_{11}$; mol wt 673.79. C 64.17%, H 7.63%, N 2.08%, O 26.12%. From seed of *Sabadilla officinale* (Schlecht. & Cham.) A. Gray and also from the rhizome of *Veratrum album* L. *Liliaceae*. Can be prepd from commercial veratrine as the sparingly sol nitrate. Isoln: *J. Chem. Soc.* **1935,** 122; Vejdelek *et al.*, *Chem. Listy* **50,** 1 (1956); *Coll. Czech. Chem. Commun.* **22,** 98 (1957). Isolation and properties: L. C. McKinney *et al.*, *Anal. Biochem.* **154,** 33 (1986). Toxicity studies: O. Krayer *et al.*, *J. Pharmacol. Exp. Ther.* **82,** 167 (1944); K. Tanaka, *ibid.* 113; Swiss, Bauer, *Proc. Soc. Exp. Biol. Med.* **76,** 81 [illegible]. Review of chemistry and structure of veratridine and *Veratrum* alkaloids: Kupchan, By, in *The Alkaloids* [illegible] F. Manske, Ed. (Academic Press, New York, 1968) [illegible]



Yellowish-white, amorphous powder. Turns in water. mp 180° (after drying at 130°). $[\alpha]_D$ [illegible] pKa 9.54 ±0.02. Insol in water. Slightly sol in alcohol. Toxicity: mice (mg/kg): 1.35 i.p. (Swiss, Bauer); 0.4 [illegible] s.c. (Tanaka).

Nitrate. Amorphous powder, sparingly sol in water.

Sulfate. Slender needles, very hygroscopic.